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Chiron Corporation Intellectual Property - R440 P.O. Box 8097 Emeryville, CA 94662-8097			LY, CHEYNE D	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary****Application No.**

09/580,380

**Applicant(s)**

GIBSON ET AL.

**Examiner**

Cheyne D Ly

**Art Unit**

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 15 December 2003.
- 2a) ☒ This action is **FINAL**.      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3, 5, 8-14, 21-24 and 75-82 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5, 8-14, 21-24, and 75-82 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_      6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. Applicants' arguments filed December 15, 2003 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.
2. It is acknowledged that claims 4, 6, 7, 15-20, and 25-74 have been cancelled.
3. The addition of new claims 75-82 has been acknowledged.
4. Claims 1-3, 5, 8-14, 21-24, and 75-82 are examined on the merits.

### **CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH**

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 5, 8-14, 21-24, and 75-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
7. This rejection is necessitated by Applicants amendments.
8. Specific claims 1 and 8, lines 12-13; 5 and 21, line 3; 78, step (e), line 2; and 81, lines 1-2, the phrase "best fit the distance constraint information" causes the claims to be vague and indefinite because it is unclear what the distance constraint information is being used to fulfill the "best fit" criteria. The cause for the vague and indefinite issue is further discussed below. Clarification of the metes and bounds is required. Claims 2-3, 5, 9-14, 22-24, 75-77, 79, 80, and 82 are rejected for being dependent from the above rejected claims.

Art Unit: 1631

9. Claims 1 and 8, lines 9-10, recite the limitation "the primary sequence of the protein".

There is insufficient antecedent basis for this limitation in the claim. Claims 2-3, 5, 9-14, 22-24, and 75-77 are rejected for being dependent from the above rejected claims.

#### **RESPONSE TO ARGUMENT**

10. Applicant argues that the instant specification (page 9, lines 7-15; 12:30-17:27; and 30:lines 6-25) provides adequate disclosure wherein one of skill in the art would not find the phrase "best fit the distance constraint information" to be vague and indefinite. Applicant's argument and pointed to support has been fully considered and found to be unpersuasive as discussed below.

11. Specific to the pointed to support, the specification further supports that the recitation of the limitation of "best fit the distance constraint information" causes the claims to be vague and indefinite. For example, the instant specification discloses distance constraint information to include binding proximity, functional groups, and spacer arms differ in lengths and flexibilities, which individually determines the distance constraint. What distance constraint information is being applied to determine that a conformation "best fit the distance constraint information." Therefore, pointed support does not help Applicant overcome the vague and indefinite issue of the above rejected claims.

#### **CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH**

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1631

13. Claims 1-3, 5, 8-14, 21-24, and 75-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using equation of claim 24 to determine the tertiary structure (3D) of a macromolecule such as a protein by cross-linking the said protein for analysis by mass spectroscopy, does not reasonably provide enablement for the determination of the tertiary structure (3D) of a macromolecule such as a protein by any other methods (X-ray crystallography etc.) or mathematical equations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. This rejection is maintained with respect to claims 1-3, 5, 8-14, and 21-24, as recited in the previous office action mailed August 26, 2003. The instant rejection has been extended to new claims 75-82.

15. This rejection is necessitated by Applicants amendments.

16. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic

engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

#### **RESPONSE TO ARGUMENT**

17. Applicant argues by amendment by having independent claims 1 and 8 to recite that the physical distance constraints comprise cross-links. Further, Applicant argues that the claimed invention, as presented in claims 1 and 8, embodies methods that make use of cross-link information in conjunction with other distance constraint information such as NMR data sets. The claim amendment and argument have been fully considered and found to be unpersuasive as discussed below.

18. The claimed invention embodies methods that make use of cross-link information in conjunction with other distance constraint information such as NMR data sets, X-ray crystallography, and mass spectroscopy. The claim amendment via the recitation of the physical distance constraints comprise cross-links has not changed the scope of the claims to commensurate in scope with the disclosure of the instant specification.

19. Further, the claim amendment and argument do not address the lack of enablement in scope rejection as directed to the use of the equation of claim 24 to determine the tertiary structure (3D) of a macromolecule such as a protein by cross-linking.

#### **RE-ITERATION OF REJECTION**

20. It is re-iterated that Applicant provides enablement disclosure for determining tertiary structure (3D) of a macromolecule such as a protein by cross-linking the said protein for analysis by mass spectroscopy (Examples 1-3) and generating a hypothetical structure according to the equation of Page 36.

21. It is noted that Applicant discloses that determining tertiary structure (3D) of a macromolecule such a protein can be achieved via X-ray crystallography and NMR and such techniques are unpredictable due to the difficulty of the said method (page 12, lines 13-27). Further, it is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002).

22. Further, Applicant does not provide to one of skill in the art to use any other equations to generate the hypothetical structure of the claimed invention.

23. Accordingly, it would be unpredictable for one of skill in the art to use any other techniques such X-ray crystallization or NMR beyond the method, 3D structure determination via cross-linking protein for analysis by mass spectroscopy, disclosed in the instant specification. In light of the difficulty of the art of determining 3D structure (X-ray crystallization etc), it is, therefore, unreasonable to expect one of skill in the art to use the information disclosed for one specific method, determining tertiary structure (3D) of a macromolecule such as a protein by cross-linking protein for analysis by mass spectroscopy,

Art Unit: 1631

to practice the invention with any other method (X-ray crystallization etc) without undue experimentation.

24. In light of the lack of guidance for using any other equation for generating the hypothetical structure of the claimed invention, it is, therefore, unreasonable to expect one of skill in the art to use the information disclosed for one specific equation to determine the tertiary structure (3D) of a macromolecule such as protein by cross-linking protein for analysis by mass spectroscopy to practice the invention with any other equations without undue experimentation.

#### **CLAIM REJECTIONS - 35 USC § 102**

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

26. A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

27. Claims 1-3, 5, 8, 14, 21-24, and 75-82 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lacroix et al. (1997).

28. This rejection is maintained with respect to claims 1-3, 5, 8, 14, and 21-24, as recited in the previous office action mailed August 26, 2003. The instant rejection has been extended to new claims 75-82.

29. This rejection is necessitated by Applicants amendments.

#### **RESPONSE TO ARGUMENT**

30. Applicants argument via amendment that Lacroix et al. does not disclose the limitations of providing a set of candidate three-dimensional conformations for the primary sequence of



the protein and applying physical distance constraint information to the candidate three-dimensional conformations to select one or more of said structures that best fit the distance constraint information has been fully considered and found to be unpersuasive as discussed below.

31. Lacroix et al. discloses the use of computer-assisted three-dimensional homology modeling for a set of candidate three-dimensional conformations comprising Clr B chain from chymotrypsin, trypsin, and elastase proteins (page 6272, column 1, Computer-assisted Three-Dimensional Homology Modeling § ) and the primary sequences corresponding to said proteins are disclosed in Figures 4, 5, and 8.

32. The complementary information provided by homology modeling was used (prior) to construct a three-dimensional model of the  $\gamma$ -B monomer, in which module V interacts with the serine protease on the opposite side to both the active site and the activation site (distance constraint) (Abstract etc.), as in instant new claims 81 and 82.

33. As directed to the limitation of applying physical distance constraint information to the candidate three-dimensional conformations to select one or more of said structures that best fit the distance constraint information, Lacroix et al. uses "physical distance information" such as amino acid sequence lengths and active sites derived from cross-link experiments. The method of Lacroix et al. applies "physical distance information" by superimposing residues within the limit of 1.5 Å in modeling analysis (page 6277, column 1, Homology Modeling of the Protein Modules of the Clr  $\gamma$ -B Region § ). Due to the vague and indefinite issue introduced by the new limitation (Paragraph 9) and the claim limitation not being

specific as what physical distance information is being applied to achieve the claimed invention, the pointed to citation of Lacroix et al. clearly anticipates said new limitations.

34. Specific to Applicant's argument Lacroix et al. does not disclose the limitation of a "threading program," Lacroix et al. discloses the used of the program O for the computer-assisted three-dimensional homology modeling. Due to the lack of a definition of the threading program in the instant specification, the claims have been construed to read on a threading program is a portion of a program that can run independently of and concurrently with other portions of the program as understood by one of ordinary skill in the art.

Therefore, the program O disclosed by Lacroix et al. sufficiently meets the criteria of a threading program as understood by one of ordinary skill in the art.

35. Specific to Applicant's argument that the limitation of "constructing a virtual library of proteolyzed products which library is indexed by...average mass data," it is re-iterated that Lacroix et al. discloses a virtual library of proteolyzed products as represented by Table 1, which consists of average mass data (Table 1 and page 6274, column 1, lines 18-24), as in instant claims 22 and new claim 80.

36. Specific to the limitation of claim 78, step (a), wherein "the number of cross-links in the protein is at least about 10% of the number of amino acid residues in the protein", Lacroix et al. discloses a proposed cross-linking site comprising 23 of 58 (39%) amino acid residues of a protein (Figure 5).

37. The method of Lacroix et al. applying "physical distance information" by superimposing residues within the limit of 1.5 Å in modeling analysis (page 6277, column 1, Homology

Modeling of the Protein Modules of the Clr y-B Region § ) which is about 2-5 Angstroms, as in instant new claims 77 and 79.

#### **RE-ITERATION OF REJECTION**

38. It is re-iterated that Lacroix et al. discloses a method for three-dimensional modeling based on chemical cross-linking and homology modeling (page 6272, column 1, Computer-Assisted Three-dimensional Homology Modeling §) wherein the EDC cross-linked protein is isolated and fragmented by proteolysis (Abstract et al.). The fragmented peptides are identified by mass spectrometry (page 6272, Mass Spectrometry Analysis §). The peptides are constrained as to the distance between Gly280 – Met351 from the N-terminus (Figure 5) and the sequence are determined by Edman degradation (Figure 7), as in instant claims 1-3, 8, and 78, steps (b)-(e).

39. Scoring values are assigned to fragments having specific distance (Table 1), as in instant claims 5, 20 and 21.

40. Crossed linked fragment are enriched by fractionation of the reaction mixtures (Figure 1), as in instant claim 14.

41. The virtual library of proteolyzed products is represented by Table 1, which consists of average mass data (Table 1 and page 6274, column 1, lines 18-24), as in instant claim 22.

42. The hypothetical structures of the peptides with the predicted protein folds are illustrated in Figures 9-11. Further, Lacroix et al. discloses the homology modeling is similar to that of Rossi et al. 1995 (page 6272, column 1, Computer-Assisted Three-dimensional Homology Modeling §). Rossi et al. discloses "threading" wherein a set of homologous three-dimensional structures is used as a reference template, sequence of proteins are aligned and

Art Unit: 1631

the candidate structure is identified by comparing the said structure to the reference set (Rossi et al., page 7313, Computer-Assisted Three-dimensional Homology Modeling §, columns 1-2), as in instant claims 23, 75, and 76.

### **CLAIM REJECTIONS - 35 USC § 103**

43. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

44. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

45. Claims 1-3, 5, 8-14, 21-24, and 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lacroix et al. (1997) taken with Mitra et al. (1979).

46. This rejection is maintained with respect to claims 1-3, 5, 8-14, and 21-24, as recited in the previous office action mailed August 26, 2003. The instant rejection has been extended to new claims 75-77.

47. This rejection is necessitated by Applicants amendments.

48. Lacroix et al. (1997) discloses the limitations of claims 1-3, 5, 8, 14, 21-24, and 75-77 as discussed above.

49. However, Lacroix et al. does not disclose the specific limitations of claims 9-13.

#### **RESPONSE TO ARGUMENTS**

50. Applicants argue that amended claim 8 from which claims 9-13 depend has overcome the Lacroix reference as discussed in the Rejections Under 35 U.S.S. § 102(b) arguments.

Applicant's arguments to the Rejections Under 35 U.S.S. § 102(b) have been fully considered and found to be unpersuasive as discussed above. The above response as directed to the Rejections Under 35 U.S.S. § 102(b) is being applied to Applicant's argument to overcome the instant 35 U.S.C. 103(a) rejection.

#### **RE-ITERATION OF REJECTION**

51. It is re-iterated Mitra et al. discloses the general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction §, lines 1-4) such as bifunctional reagents (page 3106, column 2, Discussion §, lines 12-13) which reaction with amines (page 3100, column 1, lines 64-65) as in instant claims 9 and 10.

52. Two reagents are synthesized wherein one reactions with a nuclease between lysine residues 7 and 37 and the other at 31 and 41 (Abstract etc.), as in instant claims 11 and 12.

53. The first cross-link is introduced to allow a new conformation for the second link to take place (page 3108, column 1, lines 9-12), as in instant claim 13. It is noted that the first cross-link reaction is optimized to introduce one cross-linker per molecule before the second cross-linker can be introduced.

54. Mitra et al. discloses reagents such as cross-linking reagents have wide application to the studies protein structure and the said agents are important tools for biochemist and molecular biologists for protein structure determination (page 3110, column 1, lines 22-30). Therefore, Mitra et al. suggests that cross-linking reagents are applicable and important tools to determining the tertiary structure of proteins such as the Clr serine protease of Lacroix et al.

55. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Mitra et al. for general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction §, lines 1-4) to use the method Lacroix et al. for determining the tertiary structure of a protein with the cross-linking reagents of Mitra et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method for three-dimensional modeling based on chemical cross-linking and homology modeling as taught by Lacroix et al. and use the said method with the cross-linker reagents as taught Mitra et al.

### CONCLUSION

56. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

57. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory

Art Unit: 1631

period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


58. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 872-9306.

59. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

60. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

61. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

C. Dune Ly  
3/2/04

  
ARDIN H. MARSCHEL  
LEGAL INSTRUMENTS EXAMINER